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United States
Environmental
Protection Agency

Science Advisory
Board (1400A)
Washington, DC

EPA-SAB-EC-02-00X

www.epa.gov/sab

Interim Review of the Particulate Matter (PM) Research Centers of the USEPA: An SAB Report

**A REVIEW BY THE PM
RESEARCH CENTERS
INTERIM REVIEW PANEL OF
THE EXECUTIVE
COMMITTEE OF THE US EPA
SCIENCE ADVISORY BOARD
(SAB)**



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460**

March 19, 2002

**OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD**

Note to the Reader:

The attached WORKING DRAFT "Interim Review of the Particulate Matter (PM) Research Centers of the USEPA: An Report" is a draft report of the EPA Science Advisory Board (SAB) that is still undergoing final SAB review. The SAB PM Centers Panel will discuss the draft on a conference call on March 27 from 11:00 to 1:00 Eastern Time. Once approved as final draft by the Panel, the report will be transmitted to the Executive Committee (EC) for action at a publicly accessible conference call in early May. Once the EC members have completed their deliberations on the document, the report will be transmitted to EPA Administrator and will become available to the interested public as a final report.

This draft is being released at this time for general information to members of the interested public and to EPA staff. This action is consistent with the SAB policy of releasing draft materials only when the Committee involved is comfortable that the document is sufficiently complete to provide useful information to the reader. The reader should remember that this is an unapproved working draft and that the document should not be used to represent official EPA or SAB views or advice. Draft documents at this stage of the process often undergo significant revisions before the final version is approved and published.

The SAB is not soliciting comments on the advice contained herein. However, as a courtesy to the EPA Program Office which is the subject of the SAB review, we have asked them to respond to the issues listed below. Consistent with SAB policy on this matter, the SAB is not obligated to address any responses which it receives.

1. Has the Committee adequately responded to the questions posed in the Charge?
2. Are any statements or responses made in the draft unclear?
3. Are there any technical errors?

For further information or to respond to the questions above, please contact:

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8 March XX, 2002

12 EPA-SAB-EC-02-00X

14 Honorable Christine Todd Whitman
15 Administrator
16 U.S. Environmental Protection Agency
17 1200 Pennsylvania Avenue, NW
18 Washington, DC 20460

20 Subject: Interim Review of the Particulate Matter (PM) Research Centers: An SAB
21 Report

23 Dear Governor Whitman:

25 On February 11 and 12, 2002 the PM Centers Interim Review Panel (Panel) of the US
26 EPA Science Advisory Board (SAB) met to review the Agency's PM Research Centers program
27 as a mechanism for generating research results that can inform Agency decision-making. The
28 request to provide this advice was received from the National Center for Environmental
29 Research (NCER) in the Office of Research and Development (ORD).

31 In 1998 the NCER, under its Science to Achieve Results (STAR) Program issued a
32 competitive request for applications that resulted in the support of five PM Research Centers for
33 up to five years, with a total of \$8M expended in the first year of the program. The Centers were
34 to address research needs in the areas of exposure, dosimetry, extrapolation modeling,
35 toxicology, and epidemiology.

37 As it considers budget formation for FY04 and beyond, NCER needs to decide whether
38 or not to continue with the concept of PM Research Centers beyond the current funding cycle, or
39 whether there might be a better way of generating the research results that will inform Agency
40 decision-making on PM issues. Insufficient time has passed for the Centers – individually or
41 collectively – to have generated a body of research results that could allow a definitive answer to
42 this question based on “outputs”, *per se*. However, considerable experience has been gained
43 with the Centers concept to date that can allow an assessment of the overall utility of this
44 approach, if not of the individual Centers themselves.

46 This emphasis on the assessment of concept of Centers-based research is reflected in the
47 Charge to the Panel that consists of an overall questions, plus six specific questions:

49 Overall Question:

50 Is it likely that the PM Centers program will be sufficiently successful to merit

continuation in FY 2004 and beyond? In which areas, to what extent, and for what reasons is a PM Centers program beneficial? Where it is not, what improvements can be made?

Specific Questions:

1. Recognizing the PM Centers program is barely at its halfway point, what important research findings (or promising investigations) have been made that would not have occurred otherwise? What unique aspect(s) of a Centers program enabled such actions to be taken.
2. To what extent has the direction or focus of research shifted as a result of the multi-disciplinary interactions within the Center (i.e., findings in one department influence researchers in another to change direction or emphasis). To what extent have changes in research direction or emphasis been influenced by Science Advisory Committee reviews, interactions with other PM Centers, or interactions with the broader PM research community? Which factors have been most influential?
3. How successful are Centers in communicating their findings to the public and specifically, to those who directly use their research? Is it clear that the work has been supported by the PM Centers program?
4. How, if at all, does a PM research centers program facilitate agreement or consensus on protocols or procedures to enable more direct comparison of results among research institutions or centers?
5. How, if at all, does a PM research centers program leverage or maximize use of resources through sharing expensive equipment, samples, data, etc.?
6. How is the program perceived within and outside the research community? Does a research center have greater visibility, and if so, what is the impact?

Detailed answers to these questions are found in the body of the report. The thrust of the answers are captured in the major findings and recommendations:

1. The PM Centers Program has both a) produced benefits beyond those normally found in individual investigator-initiated grants and b) is likely to continue to provide such benefits through to the end of its current funding cycle. Overall, the Panel found that the program merits continuation beyond FY04 -- through a new fully-competitive round of applications -- as one part of a diverse PM research portfolio at the Agency.
2. The Panel identified several specific advantages that the Centers approach offers over other traditional research mechanisms, including enhanced flexibility and adaptability leading to improved timeliness, ability to conduct higher-risk pilot and validation efforts, study designs enhanced by intra-center multi-disciplinary integration, and improved leveraging of the Agency's and the Centers' research resources, among others.
3. The Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also challenges to insure that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community. Key

1 enhancements include the following:

- 2 a. Continued attention in a new request for applications (RFA) to focusing
3 the Centers' efforts on the most critical PM needs
4 b. The development of an informal, but overarching, mechanism of
5 scientific advice to the program
6 c. Enhanced opportunities for cross-fertilization of ideas with EPA
7 intramural researchers and the broader extramural community
8 d. The provision of systems and resources from the start for inter-center
9 integration efforts.

10
11 We appreciate the opportunity to review and provide advice on the PM Research Centers
12 program. We want to acknowledge the valuable assistance of the Agency staff who supplied us
13 with information that is a part of the public record of our meeting. The presentations and
14 availability of the Center Directors to answer questions during our public meeting was also quite
15 helpful.

16
17 We look forward to your response to this report.

18
19 Sincerely,

20
21
22
23 Dr. William H. Glaze, Chair
24 Executive Committee
25 Science Advisory Board

26 Mr. Daniel Greenbaum, Chair
27 PM Research Centers Interim Review Panel
28 Executive Committee
Science Advisory Board

NOTICE

This report has been written as part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

Distribution and Availability: This Science Advisory Board report is provided to the EPA Administrator, senior Agency management, appropriate program staff, interested members of the public, and is posted on the SAB website (www.epa.gov/sab). Information on its availability is also provided in the SAB's monthly newsletter (*Happenings at the Science Advisory Board*). Additional copies and further information are available from the SAB Staff [US EPA Science Advisory Board (1400A), 1200 Pennsylvania Avenue, NW, Washington, DC 20460-0001; 202-564-4546].

**U.S. Environmental Protection Agency
Science Advisory Board
Executive Committee
Particulate Matters Interim Review Panel***

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9 * Members of this SAB Panel consist of

10 a. SAB Members: Experts appointed by the Administrator to serve on one of the SAB
11 Standing Committees.

12 b. SAB Consultants: Experts appointed by the SAB Staff Director to a one-year term to
13 serve on ad hoc Panels formed to address a particular issue.
14

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1. EXECUTIVE SUMMARY

[DFO Note: Is an Executive Summary needed in addition to the transmittal letter that is a part of the report?]

2. INTRODUCTION

2.1 Background

As one of its first and most important environmental legislative actions, the U.S. Congress passed the Clean Air Act (CAA) that authorizes the US Environmental Protection Agency (Agency) to conduct research, assess findings, and develop and implement regulations to control pollutants in the air that adversely impact human health and the environment. For the past thirty years the Agency has used this authority [modified by the Clean Air Act Amendments (CAAA) of 1990], in part, to establish a vigorous National Ambient Air Quality Standards (NAAQS) program. As a result, the Agency has implemented a costly, but effective, regulatory program to reduce the negative impacts of a series of air pollutants.

One of the key such air pollutants is "particulate matter" (PM), airborne microscopic particles of whatever composition and shape.

From the earliest days of the Agency, public support was high for the control of "dirty air"; i.e., black, sooty emissions from power plants, industrial facilities, and trucks and automobiles. This support was soon translated into regulations to monitor air concentrations and implement control of emissions that contributed to Total Suspended Particulate (TSP) matter, without a specific size classification. This standard was changed in the late 1980s to include a size criterion that included particles with mass median diameters (MMD) of 10 microns or less (PM₁₀), in recognition of the inhalability of such particles, as compared to those larger than 10 microns. Subsequent research revealed that exposures to PM at the so-called PM₁₀ standard posed unacceptable risks to human populations. As more research results became available, pressure mounted to apply additional monitoring requirements and on emissions of smaller sized PM; specifically, in the MMD 2.5 micron range, on the basis that particles of this size are more likely to penetrate to the respiratory regions of the lung and remain there for longer periods of time. The Agency and the country are currently in the process of implementing these new PM_{2.5} regulations.

Scientific research is playing a large role in monitoring and characterizing PM_{2.5}, establishing its effects on exposed populations, and developing effective control measures to reduce its concentrations in the atmosphere. Prestigious panels of experts have convened under the auspices of such groups as the National Academy of Sciences (NAS), the Agency's Science Advisory Board (SAB), and the Health Effects Institute (HEI). From these panels' deliberations a strategic research plan has emerged that will illuminate the path to making the difficult risk management decisions about regulating the sources of PM_{2.5}.

As a part of the effort to carry out this PM research plan, the Agency issued a request for applications (RFAs) in 1999 to establish five PM Research Centers, to be funded at a level of \$8M in the first year of the Centers program. As a result of the competition that drew XXX applications, the following PM Research Centers were established:

- a. Harvard University PM Center
- b. New York University PM Center

- c. Northwest PM Center
- d. Rochester PM Center
- e. Southern California PM Center

Roughly half of the five-year grant period for these Centers has passed, and the Agency must soon make a policy decision on whether or not to continue the Centers program, possibly through a second round of RFAs. The Agency has asked the SAB for its technical advice that will inform this policy decision.

There are, of course, other alternatives to conducting research via a Centers-based mechanism; e.g., awarding a large number of investigator-initiated grants. In order to evaluate the relative merits of a Centers-based program versus other alternatives, it would be helpful to have the research products from the current mechanism available to compare to the research outputs from those alternatives. In this case, however, after only two and half years, the research results from the Centers are just now beginning to appear in significant number in the scientific literature, so it is too early to assess these outputs definitively *in toto*. ~~Further, since no other alternative research mechanisms were funded, there is not an alternatively generated body of literature with which to compare the output from the Centers.~~ At the same time, sufficient experience has been gained from the Centers to date to allow a reasonable estimate of the major strengths, weaknesses, and potential of the Centers-based mechanism as a means for generating the kind of research results than will be needed by the Agency.

2.2 Charge to the Committee

Acknowledging the limitations inherent in this exercise, the SAB convened a group of experts, whose knowledge and experience -- individually and collectively -- qualify them to address the specific set of questions (the Charge) posed by the Agency.

Overall Question:

Is it likely that the PM Centers program will be sufficiently successful to merit continuation in FY 2004 and beyond? In which areas, to what extent, and for what reasons is a PM Centers program beneficial? Where it is not, what improvements can be made?

Specific Questions:

1. Recognizing the PM Centers program is barely at its halfway point, what important research findings (or promising investigations) have been made that would not have occurred otherwise? What unique aspect(s) of a Centers program enabled such actions to be taken.
2. To what extent has the direction or focus of research shifted as a result of the multi-disciplinary interactions within the Center (i.e., findings in one department influence researchers in another to change direction or emphasis). To what extent have changes in research direction or emphasis been influenced by Science Advisory Committee reviews, interactions with other PM Centers, or interactions with the broader PM research community? Which factors have been most influential?
3. How successful are Centers in communicating their findings to the public and specifically, to those who directly use their research? Is it clear that the work has

- 1 been supported by the PM Centers program?
- 2 4. How, if at all, does a PM research centers program facilitate agreement or consensus
- 3 on protocols or procedures to enable more direct comparison of results among
- 4 research institutions or centers?
- 5 5. How, if at all, does a PM research centers program leverage or maximize use of
- 6 resources through sharing expensive equipment, samples, data, etc.?
- 7 6. How is the program perceived within and outside the research community? Does a
- 8 research center have greater visibility, and if so, what is the impact?
- 9

10 **2.3 SAB Review Process**

11

12 The PM Research Centers Interim Review Panel (Panel) was recruited following

13 nominations received from SAB Members and Consultants, the Agency, and the public. The

14 Panel met in public session on February 11-12, 2002 in Room 6013 of the EPA headquarters in

15 the Ariel Rios Building at 1200 Pennsylvania Ave. NW in Washington DC. Written comments

16 from the Panelists, prepared before the meeting and modified on the basis of discussions at the

17 meeting and made available to the public, form the basis for this report. A more detailed

18 description of the SAB process for this review can be found in Appendix B.

19

20 **2.4 Format of this Report**

21

22 Following this Introduction, the report provides specific responses to the questions in the

23 Charge to the Committee (Chapter 3) and a summary of major findings and recommendations

24 (Chapter 4). A series of three appendices (a list of acronyms, a more detailed description of the

25 sab process, and an abstract) completes the report.

26

27

3. RESPONSE TO THE CHARGE

3.1 Overall Question

3.1.1 Is it likely that the PM Centers program will be sufficiently successful to merit continuation beyond 2004?

The PM Centers Program has both produced benefits beyond those normally found in individual investigator-initiated grants, and it is likely to continue to provide such benefits through to the end of its current funding cycle. Overall, we find that the program merits continuation beyond FY04 and suggest below areas where its strengths should be continued in a new round of awards and where its efforts can be enhanced.

The Centers have been and promise to continue being an important part of the PM research portfolio of the Agency. At the same time, there are clear advantages to maintaining a diverse research portfolio; e.g., by ensuring that the widest range of investigators are contributing ideas to the PM program and by providing opportunities for cross-fertilization of ideas between the PM Centers and other investigators at Agency and in the greater research community. Specifically, the Agency should continue to fund the other intramural and extramural components of the overall PM research effort. Within that overall effort, maintaining the PM Centers program in roughly the same proportion to the rest of the PM research program will enable continued benefits to flow from the PM Centers program.

To take full advantage of the benefits and collaborations afforded by a Centers program, continuation of the program should be based on a new, fully competitive RFA for any potential applicants, designed in keeping with the opportunities for enhancements described below. The Centers program should continue to be focused on addressing the PM issues relevant to the policy and regulatory needs of the Agency, including the ability of the Centers to contribute to the replication of key studies. Specific needs to which the Centers would be directed in a new round could include the same topics (i.e., exposure and health) and/or new topics (e.g., source characterization and assessment of emerging technologies). The areas should be defined by the Agency based on reviews of the priorities and accomplishments to date by the NRC Committee on Research Priorities for Airborne Particulate Matter and as part of an overall assessment of progress to date and needs that are or are not being met by all elements of the portfolio. The number of Centers to be funded should be developed within a flexible framework and determined based on a) the availability of adequate resources to provide funding, per Center, at a minimum comparable to that provided in current Centers, adjusted for inflation, and b) the availability of high quality proposals which meet the test of intensive peer review.

3.1.2 In which areas, to what extent, and for what reasons is a PM Centers program beneficial?

In its review, the Panel considered a wide range of activities underway at the individual Centers, plus the results of initial efforts at integration across Centers. Drawing on its extensive experience with the alternative to Centers-type grants -- the individual investigator grant -- the Panel identified several specific advantages that the Centers approach offered over these other

1 traditional mechanisms. These advantages include:

2
3 a. Enhanced flexibility and adaptability, leading to improved timeliness

4 From the integrated Centers report reviewed by the Panel and presentations made at
5 the meeting, it appears that the time for hypothesis generation and experimental design has been
6 decreased and that hypotheses are being "vetted" through inter-Center communication before
7 laboratory studies have been actually begun. One example of this was the decision following
8 cross-Center collaboration to initiate relatively rapidly a subchronic animal exposure experiment
9 at the NYU center.

10
11 b. Continuity for five years, allowing longer term planning and research implementation

12 In contrast to the normal project-specific grant, the Centers appear able to invest in
13 longer-term strategies on important questions; e.g., the systematic efforts by the Washington
14 Center to develop a biomarker for exposure to wood smoke and the detailed follow-up by the
15 Los Angeles Center of new exposure parameters for the Southern California Children's Health
16 Study.

17
18 c. Ability to pursue "higher-risk" efforts in methods development, validation, and pilot
19 studies, providing a greater potential for innovation

20 Efforts at methods development and validation often fare poorly in traditional
21 competitive grant programs, and yet they are essential to advancing the state of the science.
22 Centers offer the ability to undertake these efforts and, then, to field test them. In its review, the
23 Panel identified several such efforts; for example the extensive inquiry at the Southern California
24 Center into quinones exposures and effects; the development through the Rochester Center of
25 new techniques for using CT scans in dosimetry; the development at the Northwest Center of
26 new particulate carbon personal sampling techniques; and the assessment of source impacts and
27 housing factors (ventilation) on effects estimates of the PM-hospital admissions relationship
28 from the NMMAPS study and the more detailed evaluation of the harvesting phenomenon
29 conducted by the Harvard Center.

30
31 d. Improved study designs, resulting from intra-Center multi-disciplinary integration

32 The PM Centers program has allowed for the development of a critical mass in
33 interdisciplinary research at individual Centers. In concept, a Centers grant forces
34 interdisciplinary planning and coordination at the inception of study design, rather than as an
35 afterthought, thereby leveraging the value of interdisciplinary research as a whole. When
36 epidemiologists, exposure experts, aerosol scientists, toxicologists, physiologists, and other
37 scientists engage a problem collectively, there is a higher likelihood of a cohesive,
38 comprehensive approach to the research than research assembled from the ensemble of
39 individually conducted research projects at the same institutions. Just two, among several,
40 successful examples of this interaction at the current PM Centers are

- 41
42 1) The integration of toxicology and epidemiology at the Harvard Center to
43 iteratively explore the connection between potential sensitive populations
44 and the cardiac effects of PM exposure
45 2) The cross-disciplinary work among aerosol scientists, toxicologists,
46 epidemiologists, and exposure assessors to test the effects of mobile
47 source exposure at the Southern California Center.

e. Substantial potential benefits, resulting from inter-Center integration

Although the initial years of the PM Centers have been focused primarily, and understandably, on the development of integrated programs within each Center, there is some evidence of successful efforts to integrate research across Centers, especially following recent efforts by the Agency to foster this collaboration through the development of the integrated reporting for this review. Examples of these emerging benefits include the Rochester workshop on investigation of cardiac effects across disciplines, the development of pooled analyses of childhood effects in the Harvard 24-cities cohort and the Southern California Children's Health Study, and the enhanced design of panel study exposure assessment and health endpoints across all of the Centers. **[DFO note: What is this last one?]**

f. The ability for EPA and the Centers to "leverage" additional resources

~~—————The breadth of PM health effects research at most of the Centers is significant and appears to exceed the \$1.5 million/year contributed by EPA's PM Center program—in some cases by a factor of 10. Several centers provide concrete examples where the center program has allowed them to obtain additional funds. Having a 'critical mass' has made it attractive for outside funding agencies to see their questions answered in a cost-effective way, and as a result the Centers have been able to leverage their Center funding with other funding from EPA and other sources (e.g. leveraging between the Northwest Center and the EPA Cooperative Agreement exposure assessment study or the Harvard Center's use of data collected by the EPRI-supported St. Louis bus study). The existing and new studies funded by other organizations and by other EPA programs presents an important benefit to EPA, leveraging its limited funds for PM research and gaining access to the additional science generated on this broad scale.——~~

f. Demonstrated ability to "leverage" additional resources, resulting in an overall enhancement in research of interest to the Agency

The existing and new studies funded by other organizations and by other Agency programs presents an important benefit to EPA, leveraging its limited funds for PM research and gaining access to the additional science generated on this broad scale. By providing a "critical mass" of experience, interest, and expertise, a Center becomes attractive to outside funding agencies as a credible source for generating answers to their questions in a cost-effective way. Specifically, the breadth of PM health effects research at most of the Centers is significant and appears to exceed the \$1.5 million/year contributed by the Agency's PM Center program -- in some cases by a factor of 10. Several Centers provide concrete examples where their programs has allowed them to obtain additional funds: e.g. leveraging between the Northwest Center and the EPA Cooperative Agreement exposure assessment study and the Harvard Center's use of data collected by the EPRI-supported St. Louis bus study.

g. Other benefits, enhancing the value of the Centers Program

In addition to these larger benefits of the PM Centers Program, the Panel identified several other specific benefits that appear to be emerging at different Centers, including the following:

1) The ability to adapt and apply technologies/methods developed elsewhere to

the work within Center programs; e.g., the application of animal exposure techniques for concentrated ambient particles from Michigan State University to the design of similar efforts at the Southern California Center

2) The attracting of established researchers in fields other than air pollution to participate in air pollution studies; e.g. experience at the Rochester and the Southern California Centers.

3) The thoughtful and carefully planned additional use of existing epidemiology and other data bases for dose-response and other follow-up; e.g., the Harvard Center follow-up of the Six Cities data set and of the NMMAPS morbidity data set for dose-response. It is likely that this process first began at the time that the original Center proposals were prepared. This is a particular benefit of the Center approach, since under a traditional individual grant-based approach, it is unlikely that these additional analyses would have been completed due to the time pressures of investigators being required to apply continually for additional funding

In summary, it is clear that there are substantial benefits possible in a Centers Program that complement and expand upon other approaches available to EPA, both intramurally and extramurally. Given this evidence, the Panel recommends that the program be continued in a new round, so long as adequate resources are maintained to ensure the critical mass necessary to success within each Center. The Panel further suggests that this Centers-based approach may be useful in other aspects of the Agency program; e.g., the need to develop approaches to study the air pollution mixture, not just its individual components.

3.1.3 ~~Identify specific areas in which the program could be improved (in a next round of competition):~~ What improvements can be made in the Centers Program? [DFO Note: This is the Charge question.]

Having concluded that the Centers Program merits continuation, the Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also challenges to insuring that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community. Several of the enhancements suggested below aim to ensure this broader cross-fertilization of ideas.

Specifically, the Panel sees the following opportunities for continued benefits and improvement:

- a. A new RFA should seek answers to a clear set of priority research questions, based on current assessments of the state of knowledge, including those from the NRC, and the degree to which other PM investments (Agency intramural, as well as Agency and other extramural) are already meeting those needs. This was quite usefully done in the first RFA and should be continued.

b. There should be systems established and resources available, from the start, for Inter-center collaboration. The Panel noted that the request for an integrated summary report of the Centers -- which was prepared for this review -- both documented current efforts and had the added benefit of substantially increasing cross-Center communication and the identification of opportunities for integrated activities. Future Centers could be encouraged to engage in this communication earlier, perhaps with an EPA requirement for such reports on a regular basis.

c. As the PM Centers program matures, ~~Looking forward,~~ there is a need for a mechanism that could provide of overarching scientific advice and direction. Although the Panel was hesitant to recommend another layer of formal oversight, it did feel that enhanced advice and direction ~~a better overarching mechanism~~ could be achieved, perhaps through incorporation of a regular meeting of Chairs and/or participation of other “outside” representatives of the Center Advisory Committees into the annual Director’s meeting. This enhancement would

- 1) Provide opportunities for systematic comparison of results from across Centers and beyond; e.g., exposures and effects of PM from different sources.
- 2) Enable identification of new opportunities for collaboration among Centers and with the Agency and others in the research community
- 3) Ensure that the Centers do not become isolated from the rest of the scientific community and keeps abreast of the state of the science on PM issues.

~~c. To ensure that the Centers do not become isolated from the rest of the scientific community, there is a need to be regular opportunities -- perhaps as a public part of the annual Center Directors meetings -- for interaction and cross-fertilization of ideas with:~~

- ~~1) EPA Intramural researchers~~
- ~~2) The large number of other PM researchers (STAR grants, other US funding sources, Canada, Europe, etc.)~~

~~These activities could result in an additional benefit to EPA by providing a mechanism for keeping abreast of the state of the science on PM issues.~~

d. There should be expansion and formalization of the current visiting scientists program at some of the Centers in order to take advantage of the Centers as data, methods, equipment, and subject information repositories where scientists could come to focus on specific issues while utilizing Center expertise and resources.

With these opportunities for enhancement, the PM Centers Program should be able to continue to contribute substantially to the overall Agency PM Research Program.

3.2 Specific Charge Questions

3.2.1 Results to-date

1 *Q 1: Recognizing that the PM Centers program is barely at its halfway point,*
2 *what important research findings (or promising investigations) have been*
3 *made that would not have occurred otherwise? What unique aspect(s) of*
4 *a Centers program enabled such actions to be taken?*

5
6 *Q2: To what extent has the direction or focus of research shifted as a result of the*
7 *multi-disciplinary interactions within the Center (i.e., findings in one*
8 *department influence researchers in another to change direction or*
9 *emphasis). To what extent have changes in research direction or*
10 *emphasis been influenced by Science Advisory Committee reviews,*
11 *interactions with other PM Centers, or interactions with the broader PM*
12 *research community? Which factors have been most influential?*

13
14 The Panel determined that these two questions were at the core of its charge and,
15 therefore, spent the bulk of its effort having members with particular expertise (e.g., in
16 epidemiology, exposure assessment, monitoring and air chemistry, toxicology, science
17 management, etc.) review the Centers' progress, in depth, from the perspective of that expertise.
18 The results of these expertise-focused reviews are summarized in the subsections below. A
19 number of views/themes are repeated in these different reviews and provided the basis for much
20 of the overall conclusions of the Panel that generated in response to the overall charge question
21 above (see Section 3.1).

22 23 *a. Epidemiology*

24 The epidemiology studies in the Centers to date have been partly extensions of
25 ongoing studies, partly more detailed analyses of existing data bases, and partly new field or
26 panel studies, a reasonable approach given that a significant fraction of air pollution
27 epidemiology uses data collected for other purposes. The Centers program allows analysis of a
28 series of specific questions (e.g., on harvesting and threshold/non-threshold issues) that would
29 have difficulty obtaining separate grants. Therefore, the Centers program is contributing to
30 efficient utilization of ongoing studies and existing databases. Although it is hard to judge
31 whether these analyses would not have been done without the Centers program, it seems clear
32 that results are now being produced more quickly.

33
34 A further advantage of the Centers funding mechanism is the flexibility and discretion
35 that it provides to the Principal Investigator (PI) over a five-year period to direct funds in
36 interesting directions without having to go through a 1+ year grant funding cycle before work
37 can commence. This flexibility results in a very significant potential, if utilized well, to
38 accelerate the development of research findings of policy relevance. It was nicely argued by one
39 of the Center Directors, that, given the large amount of money (both on the benefits and cost
40 sides) which hinge on the regulatory decisions informed by the Centers research, there is a strong
41 societal imperative for maximum speed in the generation of policy-relevant research results. Of
42 the funding mechanisms available to EPA, the Centers approach appears to be the best
43 mechanism for achieving this speed.

44
45 Another value-added activity originating from the Centers Program is the very thoughtful
46 and carefully planned use of pre-existing data sets in follow-up analyses. It is likely that this
47 process first began at the time that the original Centers proposals were prepared, and it is a

particular benefit of the Centers approach that these follow-up analyses were completed. Under a traditional individual grant-based approach, it is less likely that these additional analyses would have been completed due to the time pressures on investigators to continually apply for additional funding. One example of this value-added activity is the planned, pooled analysis of the California Children's Health (CHS) and the 24 Cities Study. While both studies have evaluated lung function and lung function growth, the CHS was focused on the impact of mobile sources, while the 24 Cities Study was focused on the acid aerosol/sulfate Eastern air pollution mixture, thus offering the opportunity to compare health effects in areas with substantially different air quality.

Another related advantage of a Centers-based approach is the ability to pursue lines of pilot investigation which, due either to their exploratory nature or to their relatively small scale, would not be easily fundable as stand-alone grants. The Centers mechanism has made it possible to investigate a variety of important epidemiologic questions based on new analyses of existing databases. Most, though not all, of the Centers have been very effective in exploiting these unique advantages of nimbleness and flexibility in maximizing their investments in epidemiologic work.

Have the Centers made a difference in the conduct of epidemiologic research? The answer is clearly "Yes", in part, because investigators have been free to continue pursuing promising leads without having to apply for new grants. They have been able to follow new directions, that might not necessarily obtain funding in a competitive process. Examples include the following:

1. ~~The Harvard School of Public Health research on harvesting and threshold/exposure response.~~ Center funding has allowed the Harvard Center to refine and explore alternative methods, as well as the application of the methods to alternative data sets, in its research on harvesting and threshold/exposure response. The preparation, review, and awarding of proposals/contracts could have delayed the process significantly.
2. The Centers Program has enabled the Southern California Center to conduct extended analyses of the Children's Health Study as new hypotheses are introduced.
3. The Centers mechanism enables researchers to quickly address a new subject; e.g., the association between diabetes and PM pursued by the Harvard Center and the study of the association between reproductive effects and air pollution planned by the Southern California Center.
4. The Centers Program enables researchers to replicate quickly studies in one geographic area in different areas; e.g., activities at the Northwest Center. Comparisons of results from similar studies in different geographic regions can clearly provide insights into the underlying mechanisms.
5. The Centers are planning a workshop to discuss and harmonize source apportionment methodology for use in epidemiological studies. Several epidemiological studies have evaluated source category impacts. The workshop will attempt to utilize

1 more fully the available source appointment techniques and source signature data
2 to evaluate the health impacts of specific sources.

3
4 Given these strong advantages, there are several ways in which the work of Centers
5 might be further enhanced:

6
7 1. In view of the public health significance of long-term effects on survival, the effort
8 within and among the Centers to provide new insights is still somewhat limited. There has also
9 been relatively little work on the development of appropriate monitoring
10 strategies/methodologies (statistical designs, assessment of study design efficiency, sampling
11 method development) for long-term studies. Without these developments it is likely that
12 continued analysis of long-term impacts or the planning of future chronic effects studies will
13 remain opportunistic -- relying primarily on existing data such as the AIRS data or possibly the
14 speciation network data. Although the budgets of the Centers seem large, those budgets are
15 necessarily divided into many pieces in order to achieve the multi-disciplinary character that is a
16 hallmark of the Centers. As a result, there is generally not a sufficiently large amount of money
17 available for mounting a *de-novo*, stand-alone epidemiology study, which can be quite
18 expensive.
19

20 Nonetheless, there are several examples of work underway in this important area. The
21 Harvard Six Cities Study follow-up has been updated, and there has been mention that the
22 Northwest Center might investigate another cohort. There are also two examples of ongoing or
23 completed studies on school children (the Southern California and Harvard Centers) that will use
24 sophisticated exposure assessment techniques. ~~In the USC study there is a systematic effort to~~
25 ~~improve exposure assessment by stochastic and deterministic air pollution modeling, and by~~
26 ~~using GIS databases to assess effects of living close to busy roads. At NYU, one program~~
27 ~~assesses spatial variability in sulfate and fine particles.~~ **[DFO Note: This sentence is good, but**
28 **it is at a greater level of detail level than the rest of the surrounding material.]**
29

30 In sum, it seems that the Centers program is ideally suited to exchange and harmonize
31 exposure assessment efforts in the long-term studies.
32

33 2. It is important to note there is another potential side to rapid implementation of
34 changes in research; i.e., a risk of poor quality if the peer review of interim research results and
35 decisions is sped up too much. However, it is clear that informal peer review occurs in the
36 Centers via their Science Advisory Committees (SAC). The Agency may wish to consider the
37 need for a more formal system of peer review of Center studies via internal and/or external SAC
38 reviews. While this concern is not a serious problem at the moment, a more formal peer review
39 process would help to ensure that the quality of research continues to be high and is perceived to
40 so by the public.
41

42 3. It would be useful to see enhanced interaction between the research conducted at the
43 Centers and at the Agency's supersites ~~(with the obvious exception of Southern California where~~
44 ~~the leadership is already the same).~~ (The Southern California Center provides a model of how
45 this might be done.) The detailed air quality data collected at these sites should be utilized as
46 much as possible by the epidemiology community. In general, it will be important for the

1 various Centers to consider the chemical composition, as well as size, of constituents of PM in
2 their research designs.

3 4 ***b. Monitoring and Air Chemistry***

5 There are several examples of research progress that has been made as part of the
6 Centers program that would have been unlikely to occur or would have been less beneficial to
7 the overall research effort outside of such a program.

8
9 One example is the planned workshop (described in the previous section) to discuss and
10 harmonize source apportionment methodology for use in epidemiological studies.

11
12 Many of the Centers are making use of concentrated ambient particles for toxicological
13 studies. The extent of integration of this methodology, including the detailed characterization of
14 particle speciation, has been thorough under the Centers program. There has been evidence of an
15 iterative process ~~with respect to improved particle characterization for toxicological studies and~~
16 ~~for monitoring studies to have informed panel studies and toxicological work~~ in which improved
17 particle characterization from monitoring and epidemiological field studies have informed
18 toxicological studies. While it is premature to have expected a second iterative step in which the
19 results of these toxicological investigations have contributed to the development of new
20 epidemiological studies, such a positive feedback of information can be anticipated in the future.

21
22 As a result of specific Center needs, there have been initial developments of new
23 sampling techniques and extensive integration of state-of-the-art existing measurement
24 techniques in epidemiological, toxicological, and exposure investigations. Examples of new
25 methods and their immediate and extensive use in Centers research are the use of the multi-
26 pollutant personal sampler in several of the panel studies, the development of the ultrafine
27 particle concentrator, the development of new methods to measure methoxyphenols as markers
28 of wood smoke combustion, and the development of a new personal sampling method for
29 temperature-resolved carbon fractions.

30
31 Another interesting development that exemplifies the flexibility inherent in the Center
32 Program is the increased emphasis on spatial variability within the Southern California and
33 Northwest Centers. This new research direction builds upon studies conducted in Europe
34 investigating the impact of proximity to traffic sources and adds a potentially important new area
35 of emphasis for epidemiological studies which has not been considered in the time series studies
36 or the main US cohort studies.

37
38 ~~In addition to the added value areas discussed elsewhere in this review (i.e. acceleration~~
39 ~~of the research process, training new scientists, cost effectiveness, leveraging of resources,~~
40 ~~coordination of activities, improved communication with the public, flexibility, improved~~
41 ~~integration of quality control and statistical analysis).~~ Additional areas ~~can be identified~~ in which
42 the Centers program has made contributions that would not have been made otherwise include
43 the following:

44 45 1. Validation studies

46 The Centers Program makes it possible to conduct specific short-term studies
47 designed to validate or test methodology used in larger studies or to address specific research

1 questions that have arisen in larger studies. ~~These smaller studies would likely not be~~
2 ~~conducted/attempted at all outside of a major research program such as the Centers program.~~
3 Even if such short-term studies were to be contemplated under a more traditional investigator-
4 initiated research program, they would be unlikely to be supported. Examples of such validation
5 studies include a) the assessment of source impacts and housing factors (ventilation) on effects
6 estimates of the PM - hospital admissions relationship from the NMMAPS study and more
7 detailed evaluation of the harvesting phenomenon and b) the plan to replicate the multi-pollutant
8 exposure sampling in an additional location, beyond Baltimore where the initial investigation
9 was performed.

10 2. Pilot studies

11 Centers funding makes it more possible to design, develop, and test new
12 methodologies or to explore innovative hypotheses, activities which would likely be less
13 successful in an investigator-initiated grant environment. An example of this type of study is the
14 Southern California Center's work on quinones and other organic compounds that are precursors
15 to the development of reactive oxygen species. This effort has involved the development of new
16 sampling and analytical methods to link exposure assessment with toxicological investigations.

17 *c. Exposure assessment*

18 To date, exposure assessment activities have focused in four areas: 1) investigations of
19 the relationship between personal exposure to and ambient concentrations of PM; 2) resolving
20 the contributions to personal PM from indoor sources and infiltration from ambient particles into
21 indoor airspaces; 3) analysis of specific chemical components of personal PM that could explain
22 observed health effects; and 4) measurements of personal exposure to mixtures of PM and
23 gaseous pollutants. These research activities, as well as others at the PM Centers, are integrated
24 with research efforts in epidemiology, toxicology, etc., which is a major strength of the PM
25 Centers approach. Another strength is that the research, while generally integrated across
26 Centers, makes use of Center-specific environmental and lifestyle characteristics that may
27 provide further clues on exposure-response relationships. The recognition and exploitation of
28 these differences and similarities in a more integrated fashion is another strength of the PM
29 Centers.
30

31 The exposure research approaches and findings to date are not novel. Some
32 investigations have confirmed prior reports by non-Center investigators, and other investigations
33 have applied methods developed and used by non-Center investigators to their specific area.
34 Still others have used instrumentation developed by Center investigators prior to the
35 establishment of the centers. However, the advantage of exposure research at the Centers is that
36 the findings have immediacy in terms of feeding into health-related studies because of the multi-
37 disciplinary principles upon which the Centers undertake their research activities. Information
38 sharing and Center-specific internal cross-disciplinary interaction and coordination in exposure
39 research are obvious and very strong; e.g., the references to the NMMAPS and Baltimore studies
40 in the previous subsection.
41

42 The Center program is clearly allowing the Centers to improve the exposure assessment
43 component of the epidemiology studies. It cannot be stressed enough that this is where
44 important new insights will emerge that will help policy makers eventually to identify which
45 particle components, attributes, and sources are important in explaining the health effects seen in
46 epidemiologic studies. The benefits could still be greater if the Centers were to put more effort
47

1 into applying the same tools to all relevant particle exposure measurements (e.g., assess spatial
2 variability on the regional and local scale for secondary components, ultra-fine particles (UFP),
3 traffic-related components etc.)
4

5 Each of the current Centers has a research project related to exposure of various
6 populations to environmental levels of PM and co-pollutants. However, not all Centers have as
7 their primary goal conducting a large scale population study. This is probably a good approach
8 since the cost of such studies requires the diversion of significant Center resources. However,
9 these are important studies, and the cost of such studies may require funding by a different
10 mechanism (perhaps a cooperative agreement) in order to take advantage of resources available
11 from the Agency, the National Institute of Environmental Health Sciences (NIEHS), the Centers
12 for Diseases Control and Prevention (CDC), the National Institute of Heart, Lung, and Blood
13 Institute (NHLBI), and other national agencies.
14

15 The Centers program provides the opportunity for exposure scientists to share results and
16 hypotheses in forums that can effectively disseminate important ideas and results to members of
17 multiple disciplines. These can be as diverse as toxicology, epidemiology, and clinical sciences.
18 The exposure scientists provide the link between the epidemiology and toxicology studies with
19 findings of better indicators or metrics of exposure in populations at risk, which can augment or
20 replace specific PM components in toxicology evaluations; e.g organic carbon and ultrafine
21 aerosols, instead of elemental carbon and non-size segregated aerosols that were originally used
22 to examine mechanisms of exposure and response. For example, in the current Centers program
23 this integration is manifested by panel studies of exposure and health outcomes. Instead of
24 conducting a single RO1-based exposure panel study that would produce populations exposure
25 intensities and profiles, the Centers provide the opportunity to augment the usefulness if these
26 measurements by integrating them with health outcomes research. In an RO1-based approach, a
27 new grant application targeted at health outcomes would probably have to be submitted based on
28 the results on the prior RO1 exposure study. Thus, to meet the needs of national PM research
29 program, the Centers concept provides a more effective use of time and resources.
30

31 It is too early in the first funding cycle of the Centers to see clear examples of feedback
32 loops between exposure and health-related studies that change the direction of the investigation
33 in the various disciplines. At this time, the exposure assessment research efforts are guided by
34 the need to reduce uncertainty in specific areas of personal and community exposure to PM in
35 order to reduce uncertainties in health investigations. However, there are activities that may
36 result on redirection of health effects studies because of exposure research findings; e.g., the
37 finding of quinones and related compound concentration gradients.
38

39 It would seem that the exposure-related research undertaken to date, with very few
40 exceptions of still uncertain significance, would probably have been carried out without the
41 Centers. However, efficiencies in the timeliness of the research and the application of the results
42 are hallmarks of the Centers' program and would be unlikely to be achieved otherwise. It is
43 important also to recognize that there is a very large body of research on exposure to PM outside
44 the Centers. It is not clear that the Centers are as active in the incorporation of non-Center
45 research they are with intra- and inter-Center findings.
46

47 One approach to incorporating the non-Center findings would be for the PM Centers

1 Program to organize an assessment of the state-of-exposure-science and related disciplines ~~being~~
2 ~~collected and reported by investigators outside the Centers.~~ that includes work being conducted
3 both inside and outside of the Program. Such periodic examinations would help the Centers in
4 planning and conducting their research. There are other programs in the US, Europe, and
5 elsewhere that have and continue to accumulate information and results that can assist in
6 planning Centers-based activities and in the development of external collaborations.
7

8 Finally, although PM characterization activities are described as being directed at
9 physical and chemical characteristics, most of the focus is on chemical composition size
10 distribution. There are some initiatives to look at other attributes, surface characteristics being a
11 particularly important one. The Centers program is uniquely positioned to provide a “whole
12 picture” evaluation of the exposure-effects continuum. This approach needs to be enhanced both
13 in the PM characterization/exposure end of the paradigm and in the integration of the
14 multiplicity of health effects to explain alterations in physiology that can lead to early death and
15 disease aggravation.
16

17 *d. Toxicology*

18 Among the most promising aspects of the PM Centers program is the focus on
19 understanding the biological plausibility and mechanisms, dosimetry, and further identification
20 of the toxic components of PM. Addressing these issues, in the context of how epidemiological,
21 exposure, aerosol, and other sciences are woven into the picture, increases the likelihood of
22 accurately assessing the plausibility of proposed hypotheses and mechanisms. Furthermore, the
23 collective presence of elite scientists within and across the Centers seems to promote a
24 considered and consistent approach to testing and validating hypotheses. The intra- and inter-
25 Center attention on new discoveries and findings appears to force higher quality of product. This
26 implied peer presence and peer review increases the level of confidence in results reported from
27 the Center studies as a whole.
28

29 The Centers, through a series of animal and human clinical experiments, have been
30 effective in evaluating hypotheses related to inflammation and immunity and cardiovascular
31 effects due to exposure to PM at ambient levels. The inflammation pathway has been linked to
32 both acute and chronic effects. In order to test and evaluate the validity of observed results,
33 multiple Centers collaborated, through controlled interactive experiments and shared protocols,
34 in testing, for example, the effects of different particle size fractions and conducting inter-species
35 comparisons. They have also begun addressing factors of susceptibility, such as aging. The
36 outcome of this research has been a remarkable consistency and continuity in the observed
37 effects that appears to lead to unified hypotheses on mechanisms and pathways. This weight-of-
38 evidence and the need for internal consistency in understanding the observed effects is ~~possibly~~
39 the most a significant contribution of the PM Centers.
40

41 Ongoing and future efforts directed at further deciphering mechanisms for acute effects
42 appear promising and responsive to one of the critical challenges to the existing modifications to
43 the PM standard. In the future the Centers will likely address chronic and subchronic effects that
44 have previously been reported in epidemiological literature. Also pilot studies are planned to
45 address dosimetry issues and hypotheses. Addressing most of these areas has required
46 significant innovation and employment of study designs and technologies that previously had not
47 been applied to these areas. Such innovation is another major attribute of a Center-based

1 program.

2
3 It appears that preparation for this review provided a significant stimulus for inter-Center
4 collaborations in developing and evaluating biological and toxicological hypotheses. The Center
5 Directors were are to map out meaningful next steps for enhancing the collective understanding
6 and interpretations of results reported to date. Since PM and its components can have significant
7 regional characteristics, it is important for the Centers to consider exchange and further
8 evaluations of the PM itself. The relevance of PM composition and related source attribution are
9 critical to our understanding of the reported results.

10
11 **(Insert Oberdorster slide 5-Biological mechanisms from PM: From Exposure to Effects –some**
12 **description of the figure)**

13
14 The figure provides a unifying patho-physiological scheme for conceptualizing the
15 mechanisms of PM effects. This integrative picture was developed through the collaborative
16 discussions across the Centers and has provided a roadmap for larger toxicology community;
17 hence, it is a significant contribution. The central role of oxidative stress is being investigated in
18 all Centers as shown in figure 2 (**insert figure 6** for Oberdorster).

19
20 Another example of collaborative efforts that have been strengthened through the Centers
21 is the rapid initiation, development, and review of a protocol for subchronic CAPs exposure
22 studies in mice, subsequently leading to a chronic study. Such studies were not envisioned in the
23 original RFA. However, through inter-Center discussions and review, these studies were
24 identified as critical to furthering understanding of the mechanism of particle toxicity. The draft
25 protocols have been circulated for comment and refinement through the Center Directors,
26 resulting in an optimized protocol. The review process included comments and suggestions from
27 Agency scientists as well, in keeping with the extended scientific outreach that the Centers have
28 initiated.

29 30 *e. Science Management*

31 The Centers Program has allowed for the development of a critical mass of technical
32 PM expertise in interdisciplinary research at and between the individual Centers. By design, the
33 Program forces interdisciplinary planning and coordination at the inception of study design,
34 rather than as an afterthought, thus leveraging the value of interdisciplinary research as a whole.
35 In concept, when epidemiologists, exposure experts, aerosol scientists, toxicologists,
36 physiologists, and other scientists engage a problem collectively, there is a higher likelihood of a
37 cohesive approach to the research than would result from a simple assemblage of individually
38 conducted research projects. One of the PM Centers' greatest success to date is its serving as a
39 forcing function to promote this multi-disciplinary interaction from the ground up. In doing so,
40 the Centers Program has created a network of science that has the potential to achieve a broad,
41 but balanced, approach that provides an imbedded mechanism of self-critical peer-review.

42
43 Judging from information in the integrated report from the Center Directors, another
44 attribute of the Center approach is that the time for hypothesis generation and experimental
45 design has been decreased, with the added advantage that hypotheses have been vetted before
46 actual laboratory studies have begun. While this aspect may not have played a major role in the
47 programs to date, the effect is likely to be greater in the future when several new and innovative

1 studies are envisioned.

2
3 An investment of approximately \$1.5M/year/Center, while significant in total dollars,
4 should be viewed in the context of the types of studies necessary to advance this area. One panel
5 study of exposure/health alone can cost well over a \$1M. If instead of using a Centers-based
6 approach, individual grants approach had been used, either 3-5 investigators would have been
7 forced to collaborate (always a technical and administrative challenge), or the Agency would
8 have had to establish and prescribe research area priorities over the five-year period; e.g.,
9 toxicology, first, and exposure studies, next. The ability to plan for both types of studies at the
10 same time, as afforded by the Centers Program, has seemingly resulted in a far superior design.
11 In addition, this investment has been and will be advantageous to the Agency because of the
12 leveraging opportunities that arise from the Centers themselves, as well as from other on-going
13 research, and support provided by other agencies and funding organizations.

14
15 On the basis of reviewing the report from the Center Directors that was prepared for the
16 Panel, it would seem prudent to extend this program beyond FY04, to capitalize on the
17 investment made to date, and to take advantage of the apparent time efficiency that seems to be
18 demonstrated.

19
20 The request for the current SAB review seems to have motivated the type of inter-Center
21 collaboration and outreach that the Agency was hoping to achieve. This result argues for
22 instituting a requirements for an integrated annual report. It is important, however, that the
23 Center Program not become "an entitlement program" for certain institutions; rather, all
24 institutions should have to compete on their individual merits for continued funding beyond
25 FY04.

26
27 Based on the written background materials provided, there does appear to be some
28 disparity in the progress of individual Centers. Without an actual site visit and further
29 interactions with the individual Centers and their SACs, it is difficult to judge their individual
30 contributions and their progress relative to target. Such a site-specific examination is beyond the
31 scope of this particular review. ~~The concept of the PM-Centers program, however, appears to~~
32 ~~have been a success and merits continuation.~~(Redundant)

33
34 Because these particular Centers have a history of leadership in PM and health effects
35 research, their fame and reputation precedes the Centers Program. However, the Centers concept
36 has fostered the development of a critical mass in interdisciplinary research that has germinated
37 new collaborations from others within the research community, adding to the existing visibility
38 and "power" of each of the Centers. As Centers, they appear to render consistency to research in
39 PM, which has generated additional confidence in the results they report.

40
41 There is a concern, however, that if research is conducted outside the Center framework,
42 then that work may be ignored or deemed to be less important, and consequently not as well
43 received. If their success were to lead to an attitude of ~~in their exclusivity,~~ then the Centers
44 would run the risk of becoming insular and oblivious to advances made elsewhere, some of
45 which could have implications to their own work. These concerns should be monitored, noting
46 that some extra-Center interactions can be promoted through such devices as symposia and
47 workshops.

1 The Centers also provide excellent educational opportunities, allowing for the training of
2 young investigators in an atmosphere of interdisciplinary research. Those who are trained
3 outside and across the traditional disciplinary silos that have marked much of traditional training
4 and who are accustomed to collaborative research are more likely to transfer this understanding
5 to their future work. This birthing of a "next generation" of scientists is an important product of
6 the PM Centers Program that can potentially change the way research is conducted in the future
7 in all areas of environmental health.

8
9 The Centers have provided significant flexibility in which higher risk research activities
10 such as method development, validation, and pilot studies can be accommodated. This
11 flexibility has led to the development of innovative methods, designs, and technologies. Inter-
12 Center transfers and sharing of personnel and technology have provided an added opportunity to
13 validate and test these innovations. These transfers have also extended to extra-Center
14 collaborations and have the potential for broader application. It is important to encourage and
15 further enhance this important attribute and contribution of the Centers Program in the next
16 phase of the program. Some examples include the following:

- 17
18 1. New statistical methods for design of studies and analyses of results from
19 epidemiological and exposure studies.
- 20 2. Coarse, fine, and ultrafine mobile concentrators for field use.
- 21 3. Coarse, fine, and ultrafine biological sampling techniques for in vitro
22 mechanistic studies.
- 23 4. Inhalation toxicology trailers for field studies through the Los Angeles Basin
24 (Human and animal trailers).
- 25 5. Particle instrumentation unit for field PM characterization.

26 27 ***f. Policy-Relevant Science***

28 The fundamental reasons for initiating the PM Center research program sprang from the
29 science/policy debate that took place during the last review of the PM-NAAQS review and the
30 questions raised by the Clean Air Scientific Advisory Committee (CASAC) during its
31 deliberations. It was envisioned that an extensive research effort by the Agency would clarify
32 and resolve the issues, provide answers to questions raised, and assist in the next round of PM-
33 NAAQS review.

34
35 It appears that key areas of concerns that were expressed during the last review of PM-
36 NAAQS -- in particular, dose-response relationships, existence or lack of threshold for PM
37 effects, and issues related to harvesting -- that are central to future policy direction and
38 regulations, are being addressed by at least some parts of the PM Center Program, as well as by
39 investigators outside the program. Because of the critical nature and implications for future
40 policy in these matters, it would be useful if these findings were replicated and validated by
41 other investigators, inside or outside the Centers Program, per se.

42
43 There have been many projects started to address policy-relevant questions. At this
44 stage, the projects directly relevant to specific standard-setting questions have included
45 continuation and follow-up of studies underway prior to the establishment of the Centers
46 Program (e.g., harvesting, dose response, follow-up of existing cohorts), some controlled human
47 exposure work, and experiments on underlying biological questions (e.g., mechanisms of cardiac

effects). The regular interaction within and between the Centers appears to have refined these efforts. Although some portion of the work may have been possible with different funding approaches, there have been clear benefits from the Centers-based approach, especially in the toxicology and epidemiology interactions and its implications for the work on mechanisms.

The PM Centers research program has already produced some findings of policy significance. For example, the addition of work from the Centers to other studies suggests the absence of a threshold for PM effects, a finding which raises an important policy issue. Another important observation is the suggestion by the Rochester Center that ultrafine PM has effects distinct from those attributable to PM₁₀ and/or PM_{2.5}. Also, preliminary findings from the PM Centers Program support or expand upon previous findings that motor vehicle emissions appear to contribute significantly to PM health effects, that NO_x levels are associated with lung function changes in children, and that the organic portion of PM may be responsible for some of the PM effects. Such information raises some key policy and controls-related questions, such as how to reduce exposure to the most toxic PM fractions.

However, although there are substantial and innovative starts at examining individual PM sources and components (e.g. ultra-fines, metals, and quinones) at different centers, there is less coherence in how the effects of exposures a) to emissions from different sources and b) to different components and sizes of particles will be systematically compared, which is an important forward-looking policy question. To date, although some consistent findings have been reported, some intriguing findings that are not consistent between the Centers need to be followed explored further. It will be critical for policy makers to understand the reasons for these differences, if they are real. In addition, the Agency should take the lead in sorting out these differences by working actively with the SACs and the Center Directors. In this regard, it is worthwhile considering the option of creating an overarching mechanism to advise all of the Centers and to coordinate insights in cases of seemingly conflicting data.

g. Multidisciplinary and Inter-Center Integration

The STAR program is built upon the idea that the results must provide value added to the information that is being generated by the Agency, other stakeholders, and individual investigators. It may be ~~I imagine that in the end it will be~~ necessary to find metrics of success that go beyond scientific publications derived from individual studies. The Centers' research impact value weighted versus other contributions, generated via alternative funding mechanisms, will be an important barometer of success. Again, the degree to which the Centers can provide answers to multidisciplinary issues, as well as provide key changes in direction, will be very important indications that the Center's program did make a difference. An important measure of success for this program is the presentation of results and conclusions that will improve the scientific basis for the standard, and provide direction for implementation of control strategies by EPA program offices.

The Center Directors report prepared for this review reflect a good start at inter-Center collaboration. It will likely take at least another year to assess the full impact of the anticipated increases in interaction. Namely, will the intra- and inter-Centers interactions continue, leading to better science or fuller consolidation of the science that has been learned?. Such a relationship will be a key metric of success. Will "Centered-ness" achieve new exploratory research that continues along multidisciplinary lines, or will the Centers consolidate their thinking to test a

single or a limited number of hypotheses? If the tendency is toward the latter, then the effectiveness of the Centers approach may be lost, or the number of Centers could be reduced or augmented to address new or problems that would not be explored based upon the disciplines that comprise the current individual Centers. In terms of other stakeholders, it is not clear that if the way in which the Centers were established allows much flexibility for outreach to other scientists, except at the individual investigator level. Fortunately, inter-organizational efforts are usually are most effectively started by individual investigators. The members of the Centers have a history of success with inter-organizational collaborations, and their success over the course of the next year may provide information about what kinds of formal outreach programs may be required for a future RFA.

There is no clear path in the current design of the Centers Program that integrates major research findings into the development of an effective control strategy to protect public health. A future RFA needs to clearly incorporate this important task to ensure that the results are directed towards these concrete end points.

The previous RFA emphasized the need to a) set up a Center's clearinghouse function in order to share of its research information with other entities and b) develop methods of obtaining valuable information from other sources. These objectives should be a part of any future RFA, and the current Centers need to be encouraged to move in that direction.

Two of the major attributes that should characterize the Centers are synergism and broader exploration of the science, not necessarily premature consensus building among the Centers. These concepts could be effectively developed through annual workshops organized by the Centers. The workshop on cardiac effects conducted last year and the proposed workshop on receptor modeling are examples of how a forward-thinking Centers Program can move the entire PM research field forward effectively.

~~Less is said about interactions with the research community at large, but it should be noted that the Centers comprise a substantial portion of the PM research community. These people are generally well-connected and attend scientific meetings where broader results are presented. Assurance of interaction between the Centers and the overall research community is important. (This seems repetitive.)~~

3.2.2 Communications

Q3: How successful are Centers in communicating their findings to the public and specifically, to those who directly use their research? Is it clear that the work has been supported by the PM Centers program?

At this early stage, it is, understandably, difficult to judge how well the Centers have succeeded in establishing effective communications. It is noteworthy that quite a few publications have been generated to date that form a sound baseline for the direction of future efforts in the Centers program and for research in the broader research community. Many of the Centers appear to have used the popular media and community outreach effectively to publicize their preliminary findings and to respond to inquiries. It also appears that they have assembled multi-stakeholder SACs to ensure a flow of information in various sectors of the community.

1 It may be that with the infrastructure of the Centers the universities were better able to
2 feature this program as a community benefit, not singling out an individual investigator, but as
3 providing public health information to the media and public who have interests or questions
4 about PM issues. Since it is difficult to provide such a function in a cost-effective manner with
5 individual research grants, including this requirement in the RFA has reaped significant benefits.
6 It has also provided an administrative framework that could be utilized to broaden
7 communication activities to other groups; e.g. the regulated community.
8

9 One area in which there may be an opportunity for further improvement is the possibility
10 of a strategic communication plan across the Centers that would address the multiple audiences
11 that are targets for this information, including the scientific community. To date, Center-based
12 technical meetings have been planned with a year or so lag time ~~timeframe~~, similar to what ~~to~~
13 ~~report research results as~~ would happen with individual investigator-focused grants. There may
14 be advantages to thinking more broadly about this problem, especially if the directions of the
15 research continue and the findings from these studies have the expected significant implications
16 on public health. In this regard, making the annual Centers' meeting an open public scientific
17 meeting would be especially valuable in improving communication with the greater scientific
18 community. To further enhance communication, the Centers should consider including local
19 agencies representatives on their SACs, if that is not already the case.
20

21 3.2.3 Inter-Center interaction

22
23 *Q4: How, if at all, does a PM research centers program facilitate agreement or*
24 *consensus on protocols or procedures to enable more direct comparison*
25 *of results among research institutions or centers?*
26

27 The Centers appreciate the need for harmonization of protocols, and there has been some
28 attempts to do this. It is, however, a daunting task both organizationally and psychologically, as
29 scientists like to adhere to their own pet methods. If experiments are under way, then it is not a
30 good idea to try and get workers to change their protocols. However, for new studies or
31 extensions of existing studies some consideration of alternative, harmonized protocols could be
32 advantageous. A centrally held database of protocols would be efficient and effective means of
33 allowing experimenters to see what protocols are in use or under consideration at other Centers.
34 Periodic, joint meetings, addressing different subject areas, to discuss methodology issues could
35 also be undertaken.
36

37 Probably the best example to date of inter-Center interaction is the Rochester Center's
38 workshop on the cardiovascular effects associated with air pollution: potential mechanisms and
39 methods of testing. The workshop culminated in an excellent report that contained a list of the
40 various methodologies recommended and the parameters they assessed. This effort could serve
41 as a model for workshops on issues, such as particle size measurement, particle composition
42 measurement, *in vitro* toxicology models, and animal models. ~~This would be a very valuable~~
43 ~~resource for the centers and an excellent way to obtain harmonized protocols.~~ (Redundant)
44

45 There is a clear need for and benefit from increased inter-Center interaction, specifically
46 in the new panel studies being undertaken at all of the Centers. These studies mostly focus on
47 cardiovascular and respiratory endpoints and are generally of a small scale. There is much effort

1 in these studies to obtain detailed exposure data, as well as detailed health endpoint data (see
2 above). This is an advantage, in principle, and a result of the Center concept, in fact. However,
3 there is a potential problem with statistical power and with generalizability arising from a
4 collection of individual studies. Panel studies limited to several hundreds of observations are
5 susceptible to producing "noisy" associations, which may vary from study to study or from study
6 period to study period. Also, because of the level of detail in the exposure and health endpoint
7 assessments, there are many associations to investigate, which increases the probability of
8 chance associations, especially in size-limited studies. The Centers Program should stimulate
9 and facilitate collaboration within and between the five PM Centers, with the goal of
10 harmonizing designs, methods of measurement, and analysis of these studies. The foreseeable
11 result would be a unified interpretation of the results of the panel studies that would be much
12 more rigorous than a post-hoc, meta-analysis of completed studies would allow.

13
14 At the same time, it should be recalled that diversity of protocols can be seen as a
15 strength. The Popperian approach [DFO Note: Reference needed?] would suggest that huge
16 amounts of data showing an effect using a single approach may not be as powerful, or as
17 persuasive, as decent amounts of data showing similar effects using different approaches.

18
19 Among the more general opportunities for enhancing this cross-center work are the
20 following:

- 21
22 a. The possible publication of a newsletter that would keep running lists of methods
23 being used and allow the Centers to identify areas of protocol exchange and
24 harmonization.
- 25
26 b. More PM Center workshops like the one organized by the Rochester Center where
27 methods can be exchanged and opportunities for ~~area of~~ protocol exchange and
28 harmonization can be identified.
- 29
30 c. Attempts to develop reference materials like the Southern California Centers efforts on
31 fine PM. This is an excellent idea with a toxin so variable as PM, especially for *in*
32 *vitro* toxicology and animal studies.
- 33
34 d. Development of a centrally held, easily accessible database of downloadable pdf files
35 of protocols.

36 37 **3.2.4 Leveraging**

38
39 *Q5: How, if at all, does a PM research centers program leverage or maximize use*
40 *of resources through sharing expensive equipment, samples, data, etc.?*

41
42 Each of the Centers -- and each of the investigators within the Center -- has specific
43 strengths in resources and expertise. There are two types of interaction that maximize resource
44 use: intra- and inter-Center interactions. There are many examples of intra-Center interaction:
45 e.g., common protocols and shared use of equipment across projects within a Center. One clear
46 example is the Rochester Center's common use of cardiac analysis, flow cytometers, particle
47 generation cores, and ultrafine concentrators across different studies.

1 There are also examples of specific strengths of one Center (e.g. sampling and analytical
2 tools and equipment) being made available to others through cross-Center collaboration. To
3 mention only three, the Harvard Center developed the concentrator that will be tested/used by
4 the Rochester Center, the Southern California Center has given PM samples to investigators at
5 other Centers, the NYU Center is gaining input from other Centers as it prepares for testing in
6 mice.

7
8 In addition, the PM Centers are identified centers of PM expertise that allow them to
9 attract additional resources to fund other studies that are closely related to the goals of the PM
10 Centers Program, *per se*; cf., the EPRI-funded study at

11 ~
12 However, there are still additional opportunities to enhance inter-Center utilization of
13 resources and expertise. Even though multi-disciplinary in nature, no Center can be equally
14 excellent in all areas. Such situations may not be even desirable, because it may not be an
15 efficient use of resources. It is important that the Centers recognize their individual areas of
16 strengths and make those available to others. This realization would increase cross-Center
17 collaborations in a significant way. This is a difficult issue for inclusion in a future RFA because
18 each applicant develops his or her own independent research program. To accomplish this there
19 probably needs to be an overall mechanism that can be derived from the existing SACs to ensure
20 that the programs in each Center are tapped for their scientific and analytical strengths in order
21 to ensure that, where possible, there is cross-linking and shared utilization of tools among and
22 between future Centers. This coordinating effort must not interfere with the completion of the
23 science proposed and developed by the Center. Their goal would be to help reduce the
24 uncertainties by improving the sensitivity or reliability of analyses. **IDFO Note: It seems that**
25 **this last sentence is out of place and could be dropped with no harm to the paragraph.**

26 27 **3.2.5 Perception and visibility**

28
29 *Q6: How is the program perceived within and outside the research community?*
30 *Does a research center have greater visibility, and if so, what is the*
31 *impact?*

32
33 As a novel approach for funding research, the PM Centers Program is being closely
34 watched on a number of fronts. The significant percentage of the Agency's total PM research
35 budget devoted to the Centers is additional motivation to observe the workings of the Centers
36 closely. Finally, the importance of the issue with which the Centers deal (i.e., the effects of PM
37 in our nation's air) insures considerable attention from a range of interested and affected parties.

38
39 Also, because each of these particular Centers has a history of leadership in PM and
40 health effects research, widespread knowledge of their work and their reputation preceded the
41 Centers Program, *per se*. However, the Centers concept has fostered the development of a
42 critical mass in interdisciplinary research that has germinated new collaborations from others
43 within the research community, adding to the existing visibility and status of each of the Centers.
44 As Centers, they appear to be maintaining the consistent quality in their research endeavours,
45 which has generated additional confidence in the results they report.

46
47 Beyond visibility in the scientific community, in general, the Centers Program has

1 provided excellent educational opportunities, allowing for the training of young investigators in
2 a non-traditional interdisciplinary manner. Such motivated young people, equipped with
3 technical skills and an appreciation of what it takes to attack a complex environmental problem
4 will be a valuable resource for the future.
5

6 One area for attention, however, may be that if research is conducted outside the Center
7 framework, it may be ignored or deemed to be less important, and consequently not as well
8 received. In their exclusivity, the Centers also run the risk of becoming insular and oblivious to
9 advances made elsewhere, some of which may have implications to their own work. These are
10 issues that should be monitored and some extra-Center interactions can be promoted through
11 symposia and workshops.
12

4. FINDINGS AND RECOMMENDATIONS

1. The PM Centers Program has both a) produced benefits beyond those normally found in individual investigator-initiated grants and b) is likely to continue to provide such benefits through to the end of its current funding cycle. Overall, the Panel found that the program merits continuation beyond FY04 -- through a new fully-competitive round of applications -- as one part of a diverse PM research portfolio at the Agency.
2. The Panel identified several specific advantages that the Centers approach offers over other traditional research mechanisms, including enhanced flexibility and adaptability leading to improved timeliness, ability to conduct higher-risk pilot and validation efforts, study designs enhanced by intra-center multi-disciplinary integration, and improved leveraging of the Agency's and the Centers' research resources, among others.
3. The Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also challenges to insure that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community. Key enhancements include the following:
 - a. Continued attention in a new request for applications (RFA) to focusing the Centers' efforts on the most critical PM needs
 - b. The development of an informal, but overarching, mechanism of scientific advice to the program
 - c. Enhanced opportunities for cross-fertilization of ideas with EPA intramural researchers and the broader extramural community
 - d. The provision of systems and resources from the start for inter-center integration efforts.

APPENDIX A - ACRONYMS

1		
2		
3		
4	Agency	US Environmental Protection Agency
5	AIRS	
6	CAA	Clean Air Act
7	CAAA	Clean Air Act Amendments
8	CAPs	
9	CASAC	Clean Air Scientific Advisory Committee
10	CDC	Centers for Disease Control and Prevention
11	EPRI	Electric Power Research Institute
12	FY	Fiscal Year
13	HEI	Health Effects Institute
14	NAAQS	National Ambient Air Quality Standards
15	NAS	National Academy of Sciences
16	NCER	National Center for Environmental Research
17	NHLBI	National Heart, Blood, and Lung Institute
18	NIEHS	National Institute of Environmental Health Sciences
19	NMMAAPS	
20	ORD	Office of Research and Development
21	PM	Particulate Matter
22	PM2.5	Particulate Matter in the range of 2.5-10 micron
23	PM10	Particulate Matter of larger than 10 microns
24	RFAs	Request for Applications
25	RO1	
26	SAB	USEPA Science Advisory Board
27	SAC	Science Advisory Committees (at each of the Centers)
28	UFP	Ultra-Fine Particles\
29	UWA	
30		
31		

APPENDIX B

A MORE DETAILED DESCRIPTION OF THE SAB PROCESS

After receiving the Charge from the Agency in the summer of 2001, the SAB Staff initiated a process for soliciting the names of candidates whose expertise would allow them to make substantive contributions to answer the Charge questions. This solicitation included

- a. Contacting various individuals within EPA
- b. Publishing a notice in the Federal Register (Oct. 10, 2001, 51661-51662).
- c. Contacting knowledgeable SAB Members and Consultants

The process (referred to as the WIDECAST) garnered 48 names, several being mentioned by more than one source.

After further discussions, the SAB Staff Director contacted Mr. Daniel Greenbaum, President of the Health Effects Institutes who agreed to serve as chair of the Panel. Having established Mr. Greenbaum's available dates to hold a face-to-face public meeting, SAB Staff contacted all of the members on the WIDECAST and, after briefly explaining about the SAB and the proposed interim review of the PM Centers, inquired as to their interest and availability.

The 14 individuals who responded positively, submitting their public curriculum, became at part of the penultimate "Short List". In each case, the CV was used to construct a "biosketch" the candidate that described the individual's current position and affiliation, expertise and experience in the matters at hand, experience on other advisory committees, particular association with any of the PM Centers, and Sources of research funding. The biosketches were sent to the candidates for approval, after which they were posted on the SAB Website (www.epa.gov/sab) for any comments that members of the public might want to make that could help inform the Agency's final Panel selection. The SAB Staff Director made the final selections, conferring with the Panel and with the Executive Committee Chair (Dr. William Glaze). Primary consideration was given to expertise that the individual brought to the Charge questions; specifically, areas of epidemiology, toxicology, exposure, science program management, and policy-relevant science. An additional consideration was the benefit of having some Panelists who were members of one or more the advisory committees associated with each of the Centers. Such "inside insight" could be valuable to Panel as they grappled with how the Centers "work" and what impact they have had or could have. One of the Panelists selected has competed unsuccessfully in the Centers program, thereby bringing another perspective to the Centers experience.

The 12-person Panel roster was announced on the SAB Website. In the days before the meeting, complications arose for one of the members who had to withdraw; hence, the final Panel of 11 Members (including the Chair).

Agency staff transmitted the review materials to the Panelists in late January, consisting of the following:

- a. Charge to the Panel
- b. "The EPA's Particulate Patter (PM) Health Effects Research Centers Program", prepared by the directors and Senior Associations of the five PM Centers
- c. Response to the Charges questions, prepared by each of the PM Centers
- d. The Request for Applications (RFA) that announced the creation of PM Research Centers Program
- e. Information about Center-sponsored workshops

1 f. For each of the five Centers

2 1) Program Abstract

3 2) Progress Report

4 3) Publications List

5 On February 5, 2002 the Chair, Mr. Greenbaum, convened a conference call of the Panel
6 to discuss

7 a. The Charge

8 b. The review materials

9 c. Areas that the Agency and PM Center Directors should emphasize in their oral
10 presentations

11 d. Writing assignments (Lead Discussants) for the meeting.

12 e. Administrative matters
13

14 No public comments on the PM Centers were received prior to the meeting nor presented
15 at the meeting.
16

17 At the public meeting, the Agency presented some background material to set the context
18 for the review. This information was followed by presentations by each of the Center Directors,
19 who were available to answer additional questions, as needed during the course of the
20 deliberation. Panelists used their written comments on the Charge questions to initiate the
21 discussion. These comments were modified to reflect the sense of the entire Panel as it emerged
22 from the discussion. At the end of the meeting, the Chair summarized the answers to the Charge
23 questions and the major findings and recommendations.

24 Following the meeting, the Chair edited the draft generated by the Panel at the meeting.
25 After circulation and comment from the Panelists, the penultimate draft was discussed on a
26 conference call on March 27, 2002. The Panel-approved draft was sent to the SAB Executive
27 Committee (EC) for action during a publicly accessible conference call on At the meeting
28 the Executive Committee approved the report, subject to final approval by designated vettors..
29 This report was forwarded to the Administrator on
30
31
32

APPENDIX C - ABSTRACT

The PM Centers Interim Review Panel (Panel) of the US EPA Science Advisory Board (SAB) met on February 11-12, 2002 to review the Agency's PM Research Centers program as a mechanism for generating research results that can inform Agency decision-making. Its major findings and recommendations were as follows:

1. Overall, the Panel found that the program merits continuation beyond FY04 -- through a new fully-competitive round of applications -- as one part of a diverse PM research portfolio at the Agency.
2. The Panel identified several specific advantages that the Centers approach offers over other traditional research mechanisms, including enhanced flexibility and adaptability leading to improved timeliness, ability to conduct higher-risk pilot and validation efforts, study designs enhanced by intra-center multi-disciplinary integration, and improved leveraging of the Agency's and the Centers' research resources, among others.
3. The Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also challenges to insure that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community.

Keywords: Particulate matter, PM, research, Centers